

Genetic pathology

Lec. 2

Cytogenetic disorders involving autosomes:

Cytogenetic:

Its branches of human genetic which deal with direct examination of human chromosome and correlated with phenotype.

- **Genotype:** Is the genetic constituent of individuals.
- **Phenotype:** Is the general appearances of individuals which depend on genotype and environmental factors.

Autosomal abnormalities syndromes:

e.g. include the following:

- 1. Down's syndrome (Trisomy 21).***
- 2. Edward's syndrome (Trisomy 18).***
- 3. Patau's syndrome (Trisomy 13).***

This is the most common chromosomal disorders (one in 800 births).

- **Karyotypic features** (Karyotype writing) we have many types:

1. Regular Down's: Trisomy 21

- About **95 %** of cases have a complete extra chromosome 21 (47, XY, + 21).

- The influence of this form is strongly influenced by maternal age:

- 1 in 1550 births in women under 20 years.
- 1 in 25 births in woman over 45 years.

2. Translocation Down's:

- This constitutes about **3 %** of cases of born Down's syndrome.

- Karyotype writing in this type:

1. Mention the number of chromosome first. Then

2. Mention the sex of patient. Then

3. Mention the sign of translocation (t) because there is an extra chromosome. Then

4. Mention the number of two chromosomes sharing in this translocation in between two brackets with a slash in between.

So it write as following 46, XY, t(14/21) or t(15/13) in order of decreasing frequency.

3. Isochromosomes 21:

- This constitutes about **1%** of cases of born Down's syndrome.
- Isochromosomes of the long arm of chromosome 21 may take place result in Down's syndrome.
- Karyotype writing in this type:
 1. Mention the number of chromosome first. Then
 2. Mention the sex of patient. Then
 3. Mention the sign of isochromosomes (i) .Then
 4. Mention the number of chromosomes causing the isochromosomes. Then
 5. Followed by the symbol of the arm whether short arm "P" or long arm "q".

So it writes as following 46, XY, i21 q

Or 46, XX, i21 q

4. Mosaics:

- This constitutes about **1%** of cases of born Down's syndrome.
- They have mixtures of cells with normal chromosome numbers and extra chromosome 21.
- Karyotype writing in this type is with every line or type of Karyotype on the same principles above then separating them by a slash i.e. write the mosaics down's of normal Karyotype and another with translocation
46 XY, / 46 XY, t (14/21). Or
46 XX, / 46 XX, t (14/21).

Clinical features:

1. Most important features are **Mental retardation** which is a constant features and it's sever.
2. **Facial profile:** Flat with oblique palpebral fissures and epicanthic fold.
3. **Congenital heart disease** especially septal defect.
4. **10-20 Fold increased risk of developing acute leukemia.**
5. **Serious infections** resulting from abnormal immune response.

Structural abnormality of chromosome:

Cri-du-chat syndrome:

- It represent one of the syndrome occur due to structural abnormality in chromosome.
- Karyotype features: **Deletion** of the **short arm of chromosome 5** (5q-).
- Clinical features:
 1. A mewling (i.e. cat like cry).
 2. Sever mental retardation.
 3. Congenital heart disease.
 4. Survival of the some to adult life.

Cytogenetic disorders involving sex chromosome:

Imbalances of sex chromosome are **better tolerated** than similar imbalance of autosomes and hence sex chromosome disorders are more common than Autosomal disorders.

The milder nature of X-chromosome aberrations is in part related to the inactivation of

X-chromosome, explained by the **Lyon hypothesis.**

- All but one X-chromosome is genetically inactive.
- Random inactivation of either paternal or maternal X-chromosome occurs early in embryogenesis and lead to the formation of a Barr body. This X-inactivation is regulated by the X-inactivation specific transcript gene.

Normal females are mosaics, having two cell populations, one with inactivated paternal X and other with inactivated maternal X.

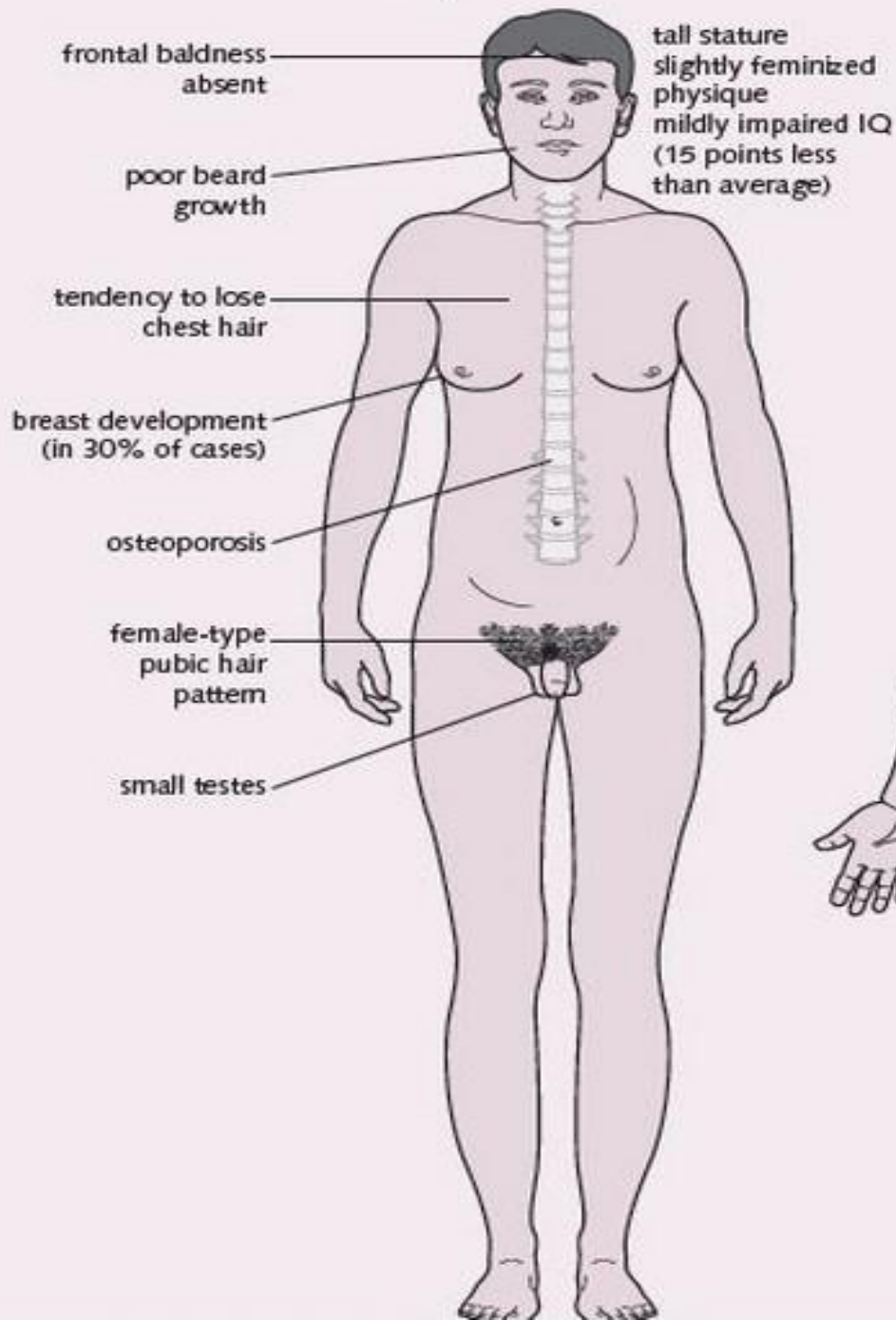
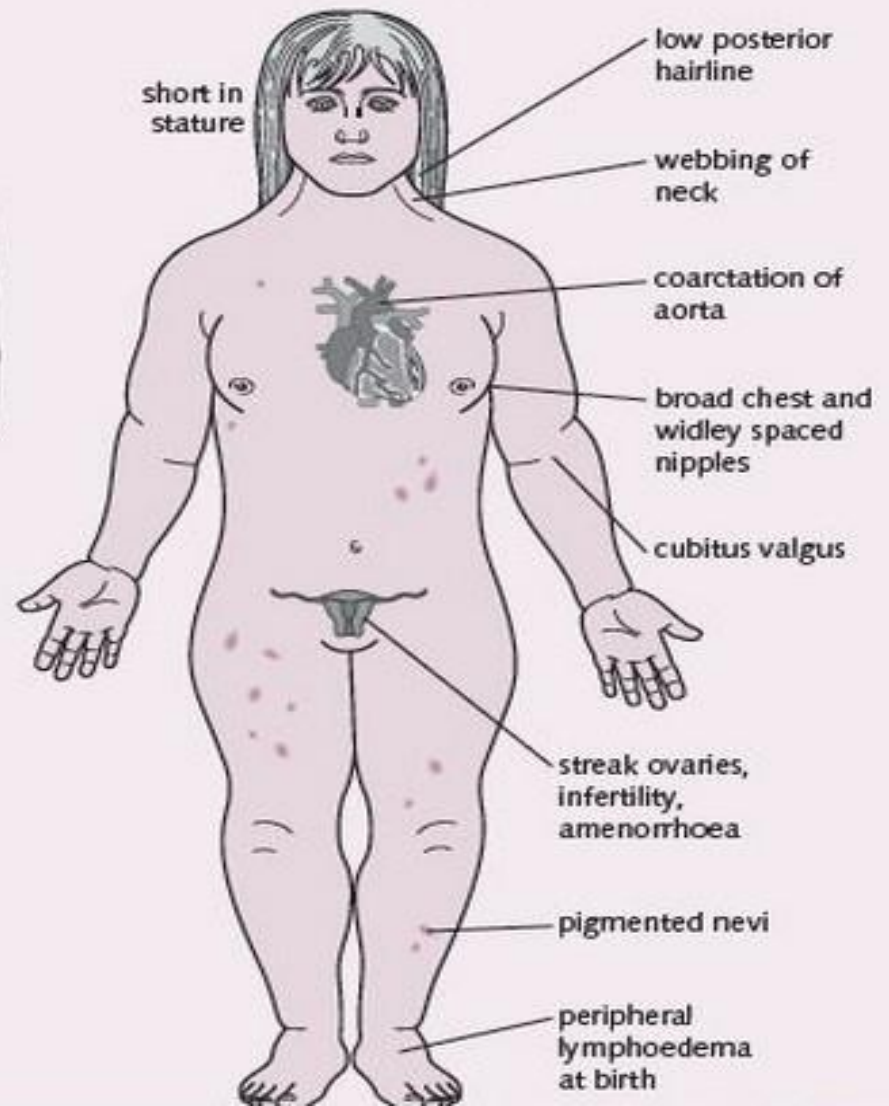
Definition: Male hypogonadism associated with two or more X-chromosome and at least one Y-chromosome.

Karyotype: 47, XXY.

Phenotype: Male.

Clinical features:

- Leading causes of male infertility.
- Minimal or no mental retardation.
- Failure in male secondary characters.
- Gynecomastia.
- Female distributions of hair.
- Atrophic testis with hypoplasia of Leydig cells.
- Plasma FSH and Estrogen levels elevated, Testosterone levels are low.

A**Klinefelter syndrome****B****Turner's syndrome**

Turner's syndrome (45, X)

Definition: Hypogonadism in phenotypic female resulting from complete or partial Monosomy of X-chromosome.

Karyotype: 45, X. most common.

Phenotype: Female.

Clinical features: ____

- Lymph edema of the neck, hand and feet.
- Webbing of the neck.
- Short stature.
- Broad chest and widely space nipple. .
- Primary amenorrhea. .
- Failure of development of breast.
- Infantile external genetalia.
- Ovaries are severely atrophic and fibrous.
- Congenital heart disease, particularly aortic coarctation.

Hermaphroditism and Pseudo-hermaphroditism:

True hermaphroditism:

- Extremely rare, these have both ovaries and testis, either combined as an ovotestis or with one gonad on each side.
- 2/3 have 46 XX Karyotype with translocation of the Y chromosome to the X-chromosome or autosomes.
- The remaining 1/3 are mosaics.

Females Pseudo-hermaphroditism:

- These have 46, XX Karyotype.
- Ovaries and internal genitalia are normal but external genitalia are ambiguous or virilized.
- The most common cause is an appropriate exposure to androgenic steroids during gestation.
- The condition may occur in congenital adrenal hyperplasia or in the presence of androgen-secreting maternal tumor.

Males Pseudo-hermaphroditism (Testicular feminization syndrome):

- There have 46, XY Karyotype.
- Y-chromosome is present and therefore the gonads are exclusively testis, but external genitalia are either ambiguous or completely female.
- The condition is result from defective virilization of the male embryo due to reduce androgen synthesis or resistance to action of androgens.
- The most form is complete testicular feminization associated with mutation in the structural gene for androgen receptors.

Single gene diseases (Unifactorial diseases):

- These are usually caused by mutation in the gene.
- Gene may behave as dominant i.e. when one of the alleles become mutated , it results in genetic disease or they may behave as recessive i.e. the disease not manifested unless both alleles are affected by same mutation.

A third category of gene is those which determine an Autosomal character but are situated on the sex chromosome (sex-linked).

Why some genes act as dominant manner,
while others behave in recessive fashion??????

To answer this question, one has to consider
and always remember the following principal:

A single gene is responsible for formation of a signal type of protein but since proteins are made up of units called polypeptides that could be the same or different in the molecules of a given protein. The principle becomes: a single gene is responsible for the formation of a signal type of polypeptides and if we know that our body structure and function from the moment of post fertilization to the full maturity and later on are determined by proteins one can understand how genes function.

These types of proteins are varied, they could be:

1. Structural proteins.
2. Immunoglobulin.
3. Single proteins produced by many oncogens.
4. Receptors.
5. Enzymes.
6. Hormones.

Therefore the action of gene whether being dominant or recessive is determined by the type of protein it produces and its function.

Dominant genes:

Usually these genes produce two types of proteins:

1. Major structural protein (e.g. autosomal dominant (AD) porphyria disease with deficiency of α -levulenic acid synthesis enzyme which undergoes mutation).
2. Enzymes (e.g. autosomal dominant familial hypercholesterolemia, disease where the receptors for LDL are mutated).

Recessive genes:

These are protein enzyme, which usually precipitate in catabolic pathways and when both alleles are defective, there is no protein i.e. no enzymes and therefore the catabolic pathway is obstructed with the accumulation of biochemical substrate.

e.g. of these are diseases of mucopolysaccharidosis, lipidosis, and phenylketonuria (PKU).

Accumulation of the substrate in sensitive tissues will result in disease state.

Sex-linked diseases:

Because most of the genes are carried on the "X" and very few are present on the "Y", sex-linked diseases refers usually to "X" linked both dominant and recessive.

In this type of inheritance, there is a lot of deviation from the expected and their explanation is forwarded by hypothesis known as Lyon's hypothesis e.g. in clinical practice, both hemophilia and G6PD- deficiencies are diseases caused by sex-linked genes which are receive in nature i.e. only males who carry the mutated gene on their "X" are affected clinically while carriers females are usually clinically silent but transfer the disease to their sons.

Sometimes, however, cases both diseases are manifested in females, this explained along Lyon's hypothesis, which states that in a females Autosomal cells, all the "X" chromosome will be inactivated except on which remains active during interphase.

- This process of inactivation takes place early in the post-fertilization period (19-20 days post-fertilization).
- The process of inactivation is random concerning the origin of the inactivated "X" i.e. either paternal "X" which come from the father or maternal "X" that come from the mother.
- All the daughter cells that descend from the affected cells harbor the same inactivated "X".

This mean that 50% of the X-chromosome is inactivated but this does not necessarily involve all the maternal X, in some areas the paternal "X" is being inactivated while in others areas it's the maternal "X" being inactivated, therefore the body of the female is a mosaic concerning the function of the active X.

So in heterozygous female for G6PD enzymes A and B, examination of different parts of her body for the type of enzyme will reveal either type A or B but never both, in any one part of the body, in contrast a male harbors either A OR B.

A female who carries that mutated gene for X- linked and present clinically the disease, it happens by chance that most parts of her body the "X" that carries the mutated gene remain active, which result in deficiency of the products of the gene → disease.

This is because of the randomness of the inactivation. Those females are known as manifesting carriers in clinical practice.

Etiology:

All single gene disease due to mutation, they are of different types:

1. Single point mutation: This is the commonest. This usually results from change in one of the nucleotide bases that form the trios (three bases), each of which codes for a specific amino acid in the protein molecules.

Not all of these changes will results in mutation that cause a disease.

2. Additional- deletional mutations.

3. Unequal crossing over: Usually during crossing over at mitosis or meiosis, the chromosome aligns themselves side by side. These processes should be very precise so that one allele would be in front of its brother alleles and even the bases are matched to each other in number.

So when there is crossing over and exchanges of chromosomal segments, no disturbances occur in the newly formed chromosomes or genes. But if the alignment is improper, then the alleles are pushed away from each other to a certain degree.

This situation take place in sites of the DNA where there are grouping of the genes of similar DNA structure with very slight variation in base structure, so one gene is mistaken for a different gene as being its allele and if crossing over occurs, then a defect will result leading to formation of two unbalanced homologous, one contain more genes and another contain less genes with both contain a hybrid gene.

Non-traditional genetic diseases:

1. Mitochondrial:

Mitochondria are organelles that produce energy by bioelectrical methods i.e. through a series of biochemical pathways catalyzed by enzymes.

The mitochondria have DNA in their structure and they are able to produce their own protein (enzymes).

The electron or energy produced is transferred outside the mitochondria by a series of biochemical reactions through interaction between different types of carrier proteins.

Mutation in the DNA of the mitochondria will result in changes of the proteins produced by these mitochondria.

The result is defects in energy production that will be reflected on the highly vital organs of the developing fetus and child leading to diseases status. These diseases are called ***mitochondrial diseases*** since only the mother supplies most of the mitochondria in the egg cytoplasm; these diseases are usually inherited from the maternal side of the family.

2. Gonadal mosaicism:

The gonads of either parent may carry a mosaic of cells, some contain a mutant gene where as others carry the normal gene. Therefore, if the gamete arises from the section that contains the mutation then a child having a genetic disease will be produced while if it arises from the sector with the normal gene, then a normal child will be produced. This type of genetics explains the presence of children affected by an Autosomal dominant disease in a family with negative history of the same disease.

3. Uni-parental disomy:

The phenomenon of uni-parental disomy is due to inheritance of both chromosomes of a pair from one parent (either the mother or the father).

There are genetics syndromes that have different clinical pictures but genetically sharing the same lesion.

Prader-Willi syndrome shares with Angelman syndrome the same cytogenetic lesion but in Angelman syndrome there are in addition ataxia and seizures.

Thanks